CASE REPORT

Histological status of the liver in relation to serum aminotransferase levels in patients with chronic hepatitis C

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Abstract

Introduction: **The diagnosis of chronic hepatitis C is based on serological, biochemical and histological parameters. However, the correlation between the activity of liver enzymes and the degree of histomorphological damage may be very poor. It has been recognised that serum aminotransferase levels do not accurately reflect the extent of liver inflammation.**
Objectives: **The aim of this retrospective study was to determine the predictive value of ALT, AST levels and AST/ALT ratio compared to histological grading and staging in patients with chronic hepatitis C.**
Material and methods: **We analysed data of 58 chronically HCV-infected adult patients who had udergone core needle liver biopsy.**
Results and conclusion: **In our study, most patients with chronic hepatitis C manifested with only mild histological findings. Although liver enzymes levels in general corresponded with the activity of the disease, even a normal level could not exclude a serious histological liver damage. Therefore, these facts should remind the physicians to perform a liver biopsy prior to therapy *(Tab. 3, Ref. 19)*. Full Text (Free, PDF) *www.bmj.sk*.**
Key words: chronic hepatitis C, grading, staging, ALT, AST, AST/ALT ratio.

Chronic hepatitis C is one of the most frequent and most important liver disorders worldwide. The diagnosis is based on examination of virological (serum HCV-RNA and anti-HCV antibodies), biochemical (especially ALT — alanine aminotransferase and AST – aspartate aminotransferase) and histomorphological parameters. Liver biopsy is not strictly necessary to determine the diagnosis, but it is considered as the "gold standard" for the evaluation of grading (degree of necro-inflammatory activity) and staging (degree of portal fibrosis) of the disease (1, 2). Among all potential prognostic variables, these two histological parameters appear to be the most reliable. Patients with mild hepatitis and limited fibrosis progress slowly or not within a 10- to 20-year period, while those with moderate and severe necro--inflammation and fibrosis progress inevitably to cirrhosis over a 20- and 10-year period, respectively (3). Although clinical markers and biopsy findings are prognostically very important, in contrast to other chronic inflammatory disorders, chronic hepatitis C represents a difficult clinical problem. This infection is often accompanied by a poor correlation between histomorphological and clinical parameters of disease. In chronic hepatitis C, the increase in alanine and aspartate aminotransferases is usually less than 5-times the upper limit of normal (ULN) and ALT levels are higher than AST in most cases. Hepatic damage is generally less prominent in patients with lower serum enzymes compared to higher levels, but a small subset of patients with normal enzymatic activity can have histologically advanced stage of disease. There are approximatelly 20–30 % of infected individuals with normal serum ALT levels and another 40 % with 2--times lower ULN, where either severe tissue lesions or permanent structural damage is present (2, 4, 5, 6).

Based on these facts it is obvious that prior to initiating an antiviral therapy, liver biopsy is usefull and in many cases very important. Physicians should know what exactly they are treat-

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ing. They should be aware of the actual morphological findings in the liver, because they never treat "serological or biochemical findings" of patients.

The aim of this retrospective study was to analyse serum ALT, AST levels and AST/ALT ratio in patients with verified chronic hepatitis C and their correlation to histological grading and staging of core needle biopsy samples.

Material and methods

The patients included in this study were patients with chronic HCV infection and positive for anti-HCV antibodies (performed by enzyme-linked immunosorbent assay ELISA-2, confirmed by Western blot test) and HCV-RNA (deteced by polymerase chain reaction – PCR) in serum. All participants were also tested for hepatitis B surface antigen (HBsAg) and antibody to anti-HBsAg, but no HBV/HCV combination was found. The qualitative evaluation of viremia and viral genotype were not included in the study. In most individuals, the exact time when that they became affected was unknown. None of the patients had a history of long-term alcohol consumption or other chronic liver disorder.

The group consisted of 58 adult patients (28 males, 30 females) with the age ranging from 19 to 64 years (mean age 46.5), who underwent a liver biopsy and were hospitalised and treated (with standard combination of pegylated interferons and ribavirin) at Clinic of Infectology in Martin. All liver tissue samples were obteined from percutaneous (blind) core needle biopsy (needle Hepafix 1.6 mm) before initiating the therapy and without repeating the biopsy after therapy. The biopsy samples were fixed in buffered formalin, embedded in paraffin blocks, stained with hematoxylin-eosin and special histochemical methods and after a complete processing examined by two pathologists – specialists in hepatology. In addition to standard hematoxylin and eosin staining, we used also special histochemical methods (Masson, Gömöri, PAS, PAS-diastasis, Perls methods) for better microscopic examination of the tissue. Serum ALT and AST levels were received at the time of biopsy and the upper reference levels, 0,68 μkat/l. and 0,72 μkat/l, respectively, were determined. Histological grading and staging was evaluated according to Ishak,s mHAI (modified Histology Activity Index) criteria (7). Grading was classified as minimal G 1 (1–3 points), mild G 2 (4–8 points), moderate G 3 (9–12 points) and severe G 4 (13–18 points), staging ranged from 0 to 6 points. Statistical analysis was done by Pearson's correlation coefficient, $p<0.05$ was considered statistically significant.

Results

Necro-inflammatory activity

Grading varied from 2 to 16 points (modus 7, average value 6.3). The intensity of portal lymphocytic infiltration and the extent of intralobular necro-inflammatory changes provided the highest contribution to the "overall" grading score. "Piecemeal" necrosis was present in 37 cases. Chronic hepatitis with histological activity G 1, G 2, G 3, G 4 was observed in 9 (15.5 %), 37 (63.8 %), 9 (15.5 %) and 3 (5.2 %) of patients, respectively. The most frequent was the hepatitis with mild degree of necro-inflammatory changes.

Portal fibrosis

Staging PF 0, PF 1–2, PF 3–4, PF 5, PF 6 was manifested in 1 (1.7 %), 38 (65.5 %), 13 (22.5 %), 5 (8.6 %) and 1 (1.7 %) of patients, respectively. A mild degree of portal fibrosis (PF 1–2) with short or long connective septa without porto-portal or porto-central bridgings was dominant. We revealed only 1 case of complete cirrhosis compared to 5 cases of incomplete cirrhosis. In general, the most frequent (46.5 %) histomorphological finding was the hepatitis with mild necro-inflammatory activity combined with just a minor fibrosis. A correlation between grading and staging ($p=0.005$) was found. No significant association between the gender and grading ($p=0.9$) or staging ($p=0.5$) was observed.

Serum aminotransferases status

Serum ALT levels correlated more with grading ($p<0.001$) than staging ($p=0.012$). On average, gradual increase of ALT values was following: 1,24-times in G 1 (0.32–1.5 μkat/l), 2-times in G 2 (0.65–4.0 μkat/l), 2,3-times in G 3 (0.8–2.3 μkat/l) and 4,1-times in G 4 (1.6–4.9 μkat/l). We revealed 7 patients with normal serum ALT levels.

Serum AST levels statistically correlated with grading ($p<0.001$) but not with staging ($p=0.08$). In contrast to ALT, serum AST values were lower than ALT. On average, gradual increase of AST was following: 1,03-times in G 1 (0.48–0.85 μkat/l), 1,25-times in G 2 (0.45–3.7 μkat/l), 1,51-times in G 3 (0.65–11.8 μkat/l) and 4,9-times in G 4 (1.3–7.8 μkat/l). We observed 23 patients with normal serum AST levels and 5 patients with normal ALT and AST activity. A significant correlation between ALT and AST values ($p<0.0001$) was found. We did not observe any association of AST/ALT ratio to necro-inflammatory activity ($p=0.6$) or portal fibrosis ($p=0.9$). A correlation between the age and grading ($p=0.007$), but not between the age and staging ($p=0.6$) was found.

Discussion

Physicians must often decide to initiate the antiviral therapy in patients with chronic hepatitis C, who are asymptomatic and have normal or minimally increased serum AST or ALT levels. Number of previous reports indicate (4, 5, 6, 8) that mostly a single normal ALT level cannot exclude even an advanced liver disease or cirrhosis. We performed this study to determine whether the serum levels of these markers, which are commonly used to evaluate the degree of liver inflammation, adequately reflect the presence of active and progressive disease.

In most cases, the increase in serum ALT activity is not extreme and does not exceed ULN 2–3 folds (9). Normal serum transaminase levels cannot exclude marked histomorphological changes with necessity to indicate a therapy (4, 8).

In 12 % of patients (6 females, 1 male) with normal serum ALT and in 40 % of patients (13 females, 10 males) with normal

Tab. 1. The relationship of ALT to necro-inflammatory activity (n (%) p<0.001).

	(N) ALT	ALT<2x	ALT 2–5x	ALT>5x
G 1	3	5	1	0
G 2	4	20	12	1
G 3	0	2	7	0
G 4	0	0	2	1
	7 (12.1 %)	27 (46.6 %)	22 (37.9 %)	2 (3.4 %)

G 1–4, degrees of necro-inflammatory activity, N – normal serum ALT level

Tab. 2. The relationship of AST to portal fibrosis (n (%) p=0.08).

	(N) AST	AST<2x	AST 2–5x	AST>5x
PF 0	1	0	0	0
PF 1–2	18	16	4	0
PF 3–4	2	11	0	0
PF 5	1	1	1	2
PF 6	1	0	0	0
	23 (39.6 %)	28 (48.3 %)	5 (8.6 %)	2 (3.5 %)

PF 0–6, degrees of portal fibrosis, N – normal serum AST level

AST levels liver biopsy revealed some histomorphological damage (Tabs 1 and 2). The remaining 46.6 % of patients demonstrated serum ALT values 2 times lower then ULN, what approximatelly corresponds to literature (2, 5, 6).

Therefore, the approach to treat individuals with normal enzyme activity is controversial in clinical practice, especially with permanently normal alanine aminotransferase (PNALT). It is very disputable, what is the degree of "overall" liver parenchyma injury in this group of patients and when it becomes a pathological condiction needed an intensive medical therapy (4). Some studies (8, 10) have shown that in these cases (with higher predominance of females) the disease had been generally associated with less severe histological liver damage and lower degree of fibrosis, as confirmed by our results, too. Herve et al (8) suggested that the history of HCV infection in these individuals might be different from patients with normal ALT.

Some authors proposed (10, 11, 12) that not ALT, but AST emerged as the most important predictor of histological activity. Schiffman et al (10) found no correlation between baseline ALT activity and liver histology in patients with normal ALT levels. During the 72-week follow-up period, ALT activity increased above the upper limit of normal in 53 % of the untreated patients with normal levels of ALT. Therefore they proposed that chronic hepatitis C patients with normal ALT levels should be evaluated in a similar manner as patients with elevated ALT levels because they are at risk for developing a significant liver disease. The decision to treat these patients with peginterferon alfa and ribavirin should be based on multiple factors, rather than on ALT levels alone. Zechini et al (11) observed a statistically significant correlation of aminotransferase values to both histological parameters (grading and staging) and even stronger correlation to AST values. Assy et al (12) found a significant relationship between AST and portal inflammation, piecemeal necroses and the extent of liver fibrosis. On the other hand, serum ALT levels did not correlate to histological activity, but correlated weakly to fibrosis. Therefore these studies suggest that among other factors serum AST should be considered in performing a liver biopsy and treating patients with chronic hepatitis C.

Various studies revealed (4, 6) that approximatelly 8–20 % of infected patients with normal serum liver enzymes had evidence of marked fibrosis or a complete cirrhosis. Rýzlová et al (13) and Stránsky et al (14) revealed a minimal or mild liver fibrosis in 55 % and an advanced fibrosis in 45 % of chronically HCV-infected individuals. We also confirmed that the most frequent finding was a minor degree of portal fibrosis (65.5 %). Although according to these authors (13, 14), AST levels have shown a better predictive value to liver fibrosis progression than ALT values, we confirmed a significant association of staging with ALT but not with AST activity. The age of the patients was not an independent predictor for hepatic fibrosis in some studies (13). The correlation between the age and a degree of necro-inflammatory activity was found, but not between the age and the extent of portal fibrosis. We observed no differences in relation of gender to grading and staging. Urbánek (9) considers the histological assessment of fibrosis during initial liver biopsy at the time of laboratory confirmation of HCV infection as the most precise method to estimate a risk of progression to hepatic cirrhosis. Stránsky et al (14) considered the histological evidence of fibrosis as an impulse to initiate the antiviral therapy which can lead to the regression and improvement of histomorphological findings.

A number of studies have indicated (15, 16, 17) that clinical "danger signal", suggesting the presence of marked fibrosis, included aspartate aminotransferase higher than alanine aminotransferase – AST/ALT ratio. The clinical usefulness of the ratio of serum AST/ALT has been explored not only in chronic hepatitis C, but also in several other liver disorders.

Park et al (15) revealed that although relatively insensitive, an AST/ALT ratio≥1 was highly specific, but not diagnostic for the presence of cirrhosis in patients with chronic HCV infection. The ratio reflected the stage of fibrosis because was parallel to fibrosis but not to necro-inflammation. Anderson et al (17) confirmed, the AST/ALT ratio increased with histological progression and ratio≥1 was found predominantly in cirrhotic patients. AST remained elevated in eight out of 33 patients in whom the ALT had returned to normal during and after therapy. They concluded that both ALT and AST are useful markers for chronic hepatitis C, but AST may elevate alone, suggesting its measurement may be useful when ALT is consistently normal. Giannini et al (16) postulated that AST/ALT ratio≥1 was highly suggestive of the presence of cirrhosis, because this parameter had increased as liver fibrosis progressed.

Based on these facts, we surprisingly revealed no correlation between AST/ALT ratio and the degree of portal fibrosis.

Tab. 3. The relationship of AST/ALT ratio to portal fibrosis (n (%) p=0.9).

	R<0.5	R 0.5–1	R 1–1.5	R>1.5
PF 0	0	1	0	0
PF 1–2	3	29	5	1
PF 3–4	0	12	1	0
PF 5	0	4	0	1
PF 6	0	0	1	0
	3 (5.2 %)	46 (79.3 %)	7 (12.0 %)	2 (3.5 %)

PF 0–6, degrees of portal fibrosis, R – AST/ALT ratio

The patient with a complete cirrhosis demonstrated AST/ALT ratio of 1.05 but in the group of 5 patients with an incomplete cirrhosis, 4 patients had shown AST/ALT ratio less than 1 (Tab. 3). On the other hand and similar to our results, Reedy et al (18) demonstrated that AST/ALT ratio had failed to predict the presence of cirrhosis. Imperiale et al (19) also suggested that the AST/ALT ratio may not be as useful for predicting cirrhosis in chronic hepatitis C as previously thought.

Conclusion

For the antiviral therapy of chronic hepatitis C, prior histomorphological liver examination, which provides significant information about prognosis and the urgency of treatment as well as likelihood of responsiveness, should be retained (3).

In this respect, the provision of liver biopsy still remains a very important factor in diagnosis of chronic hepatitis. The obvious indication for the antiviral treatment is a disease laboratory confirmed or minimally moderate degree of necro-inflammatory changes. It was generally concluded (1) that in these patients the progression of the disease is highly probable.

Thus, histological evaluation of liver biopsy enables the identification of patients considered to likely benefit from therapy, that means individuals with mild to moderate fibrosis and necroinflammatory activity. Similarly, those patients with minimal pathomorphological features, who don,t need an antiviral therapy or individuals with even advanced microscopical changes, but who won,t benefit from such treatment can be monitored and followed up with a liver biopsy evaluation every 3 to 5 years.

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Received June 18, 2007.
Accepted October 20, 2007.